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ART UNIT	PAPER NUMBER
1804	34

DATE MAILED: 06/02/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☑ Responsive to communication filed on 2/14/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), one (1) days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 3,4,8,9,11,12,16-18,21-29 are pending in the application.
   Of the above, claims 3,4,8,9,11,12,16-18 are withdrawn from consideration.
2. ☒ Claims 1,2,5-7,10,13-15,19,20 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 21-29 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

This application should be reviewed for errors.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 5-7, 10, 13-15 19 and 20 have been cancelled; claims 21-29 newly added; claims 21-29 are examined in this Office Action.

The provisional rejection of claims 21-29 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 8, 27 and 30 of copending application serial no. 07/467, 888 is maintained. Applicants have acknowledged the provisional rejection and wish to defer the issue until an indication of allowance. Therefore, the rejection is maintained.

The provisional rejection of claims 21-29 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 12-24 of copending application serial no. 07/803,285 is maintained. Applicants have acknowledged the provisional rejection and wish to defer the issue until an indication of allowance. Therefore, the rejection is maintained.

The rejection of claims 1, 2, 5-7 and 10 under 35 U.S.C. 112, first and second paragraphs, is withdrawn in view of the cancellation of the claims. However, note that the newly added claims necessitate some of the same rejections set forth regarding claims 1, 2, 5-7 and 10.

Claims 21-29 are rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 21-23 and 27-29, the word "agent" is vague and unclear since the nature of the "agent" is indeterminate. Further regarding claims 21 and 27, Applicants have disclosed treating excised nephritic tissue with antibodies and failed to disclose treating nephritic tissue with any and all other agents. It is not apparent that any and all other "agents" would inhibit TGF-B activity in a manner or extent similar to the antibody used. Therefore, the claim must be limited to use of the antibody.

Applicants' arguments, filed February 14, 1994, have been considered but not found to be persuasive. Applicants have argued that claim 21 is now directed to agents which have the characteristics of binding to TGF-beta and suppressing the accumulation of a TGF-beta induced component of the extracellular matrix. However, the "agent" as currently claimed also reads on a soluble receptor, for example, and therefor remains vague and unclear.

Regarding claims 21-28, the specification fails to present evidence showing that any other proteins were studied and that TGF-ß stimulates their synthesis. In addition the specification clearly states that the extracellular matrix is composed of a mixture of proteoglycans, glycoproteins and collagens assembled into a complex superstructure (page 1, lines 25-27). Thus the extracellular matrix includes many more proteins than decorin and biglycan, the two protein components actually investigated by Applicants. Therefore, the claim must be limited to the two components of the extracellular matrix actually investigated by Applicants.

Applicants have argued that PAS stains glycoproteins in tissues thus allowing one to visualize the ECM and that therefore the data do not indicate that accumulation of decorin and biglycan were exclusively suppressed. However, the specification fails to provide evidence regarding the increase or decrease in the other glycoproteins and merely because the tissue "stained" does not indicate that TGF-beta induced expression of any one particular glycoprotein over any other unless that glycoprotein was studied per se.

Applicants have failed to provide evidence as to the effects of TGF-beta on all the other ECM proteins and therefore the claims must be limited to biglycan and decorin.

Regarding claims 21-26, and word "tissue", a tissue is defined (Webster's dictionary, Ninth Edition, page 1237) as an aggregate of cells usually of a particular kind together with their intercellular substance that form one of the structural materials of a plant or an animal". Applicants have used the antibodies to cells grown in a petri dish and since such pathologies as glomerulonephritis, adult respiratory distress syndrome and cirrhosis of the liver are organismal ailments, and do not occur to cells in petri dishes, the claim language of claim 21 must be amended to reflect in vitro usage only.

Regarding claims 21 and 27, the specification discloses rats which have been experimentally induced to have glomerulonephritis with ATS. The specification further discloses a single treatment of the rats with antibodies to TGF-beta followed by examination of the removed glomeruli. There is no evidence presented in the specification that the "pathology" per se has been treated since pathology is an on-going condition and the specification merely indicates that the rats received a single treatment with antibodies. The specification fails to provide evidence to substantiate that a "treatment" comprising antibodies would be useful over the course of the disease and there is also no evidence that a single antibody treatment would be a "treatment" for the disease. There is no evidence that the single dose of antibody would cure or prevent the disease and there is no long term follow up of the effects of the single dose of antibody. Since antibodies when injected in vivo are known to have limited half-life in the circulation it is not apparent as to the efficacy or the usefulness of a single dose of antibody. The specification fails to disclose in detail the treatment regimen of the rats, including such features as the length of treatment, the amount of antibody administered, and so forth. The specification is not enabling for "A method

of treating a pathology..." for reasons set forth above. In addition, the specification clearly discloses that rats were administered antibodies raised in rabbits and the specification fails to disclose the effects of treating rats with foreign proteins. The specification fails to provide evidence of long term treatments and the effects of treatment using foreign antibodies, which would be expected to provoke an immune response. The specification is not enabling for the scope of the claims claiming "A method of treating a pathology...", for reasons set forth above.

Regarding claims 23 and 26, the claims must be limited to glomerulonephritis since Applicants have failed to show that the treatment using anti-TGF-beta antibodies would be effective in treatment of those diseases. It is not apparent that cirrhosis of the liver and adult respiratory distress syndrome (RDS) would be amenable to treatment with antibodies to TGF-beta since the etiology of many diseases is not known and although Applicants state that both cirrhosis and RDS are characterized by an accumulation of extracellular matrix, it is not apparent that the cause of the production is solely dependent upon TGF-beta production and would thus be amenable to treatment in the claimed manner.

Applicants have argued that it is not necessary for utility that the claimed method be effective at every stage of pathobiology; that the specification demonstrates the effectiveness of the invention and that effectiveness at any stage suffices for utility. However, Applicants have failed to demonstrate utility for the treatment of ARDS and cirrhosis of the liver at any stage and therefore Applicants' arguments are not persuasive.

Applicants have argued that the specification objectively enables the invention since it shows how to treat pathologies characterized by the TGF-beta induced production of extracellular matrix in a tissue by contacting the issue with an agent that suppresses the activity of TGF-beta. However, contrary to such assertions, the specification merely provides a single example apparently comprising only a single treatment. Contrary to

Applicants' arguments, the specification is not enabling for the treatment of such diseases since a single treatment one may provide unreproducible results and lacking more convincing evidence, the arguments are not persuasive.

Regarding claim 21, Applicants have disclosed that antibodies to TGF-beta will inhibit synthesis of extracellular matrix but have failed to show that the antibodies will inhibit accumulation of the matrix. Note that "accumulation" of a product, in this case, extracellular matrix, is dependent upon the rate of synthesis as well as the rate of degradation and Applicants have disclosed inhibition of synthesis and not addressed the rate of degradation. Therefore, the claim language should be amended to more clearly, and accurately, describe the process as it occurs. Note that the phrase "extracellular matrix" includes many more proteins than decorin and biglycan, the two protein components actually investigated by Applicants and that the specification fails to provide evidence that TGF-ß inhibition would inhibit the production of the other components. Therefore, the claim must be limited to the two components of the extracellular matrix or the two proteoglycans actually investigated by Applicants.

Regarding claims 21 and 27, the claim must be limited to the kidney tissue or kidney cells, since it is not apparent that lung, liver and skin cells accumulate extracellular matrix by the same defective mechanism as do kidney cells and therefore, it is not apparent that the same treatment would be effective in other tissues.

Claims 21-29 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

The rejection of claim 5 under 35 U.S.C. 112, first and second paragraphs, is withdrawn in view of the cancellation of the claim.

The rejection of claims 1, 6, 10, 19 and 20 under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to an antibody is withdrawn in view of the cancellation of the claims. Note however, that a similar argument was set forth above, concerning newly added claims 21-29.

The rejection of claim 13 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the cancellation of the claim.

Applicants have argued that claims 13-15, now claimed 27-29 will stand only provisionally rejected for double patenting upon the removal of the indefiniteness rejection. However, claims 27-29 remain rejected on new grounds for reasons set forth below.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> "A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claim 27 is rejected under 35 U.S.C. § 102 (b) as being anticipated by Flanders et al. Flanders discloses use of the antibody to TGF-beta to block TGF-beta induced collagen production in NRK cells, collagen being another proteoglycan. In addition, since the antibody to TGF-beta binds the TGF-beta, the addition of antibody decreases the amount of TGF-beta. Therefore, the reference anticipates the claim.

The rejection of claims 21 and 24 under 35 U.S.C. 103 as being unpatentable over Connor et al is maintained. The rejection of the claims as previously set forth is as follows:

Connor discloses treating an in vitro model system of intraocular fibrosis, a pathology characterized by extracellular matrix accumulation (page 1661, column 2, first full paragraph) which is known to produce TGF-ß (Abstract) by using antibodies to TGF-beta (Abstract). Connor further discloses that 84-100% of the TGF-beta activity could be blocked using specific antibodies to TGF-beta (Abstract). Connor differs from the claims in that the reference fails to disclose in vivo usage of the antibodies for treating the pathology. However, Connor clearly suggests such a treatment on page 1665, second column, last paragraph, wherein it is stated "The final determination of the role of TGF-beta in this disease process awaits the ability to block its activity and assess if this can retard or arrest fibrosis". Thus, it would have been obvious to one of ordinary skill to administer the antibodies in vivo in order to determine the therapeutic effect of the antibodies on disease progression. One of ordinary skill would have had a reasonable expectation of success in achieving retardation of the ocular disease by using the antibody to TGF-beta since the use of antibodies to target specific cells in vivo is a technique old and well known in the art and Connor clearly shows the ability of the antibody to block the TGF-beta effect in vitro. Thus, the question as to whether the antibody could reach the target site in order to inhibit the TGF-beta is rendered moot in view of the known and widely accepted use of antibodies to bind to a variety of cell types in a variety of locations.

Regarding claim 24, Connor discloses use of antibodies to TGF-beta (Abstract).

Accordingly, the modification of in vitro method of Connor by using the antibody in an in vivo treatment as further suggested by Connor is order to obtain a method for treatment of pathologies characterized the TGF-beta induced production of extracellular matrix in a tissue was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill

would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants have argued that at the time the claimed invention was made that TGF-beta was primarily understood to be a promoter of tissue repair. However, contrary to such arguments, Connor clearly discloses the correlation of fibrosis and TGF-beta levels (See Connor reference, Title and Abstract). Therefore applicants' arguments that the role of TGF-beta in pathological fibrosis was not understood and that no art at the time provided a reasonable expectation that blocking TGF-beta activity alone would be a successful method of treating pathologic fibrosis are not persuasive. Connor clearly discloses "the final determination of the role of TGF-beta in this disease process awaits the ability to block its activity and assess if this can retard or arrest fibrosis". Connor clearly had the expectation, based on his results, that blockage of TGF-beta activity would be linked to decrease of the disease.

Applicants have argued that their important contribution to the art was the discovery that inhibiting TGF-beta activity sufficed to suppress pathologic fibrosis without adversely interfering in the repair process. However, no claim claims "suppressing pathologic fibrosis without adversely interfering in the repair process" and there is no support in the specification for such claim language.

Applicants have argued that a person of ordinary skill reading the above statement would conclude that the authors were not sure what the role of TGF-beta in fibrosis was and did not know of any agents that block TGF-beta activity. However, contrary to the first argument, the authors clearly did know what the role of TGF-beta in fibrosis was since the authors discuss its role on page 1661, column 2, top paragraph beginning with "TGF-beta appears to have a particularly important role in the fibrotic process".

Applicants have argued that the Office Action contains a factual error: "...since anti-TGF-beta was shown to block activity of TGF-beta and TGF-beta was shown to increase intraocular fibrosis,...one of the activities which was inhibited by anti-TGF-beta was the blocking of ECM production". However, Applicants have misread the statement and have left out the work "In" which clearly appears in the Office Action. See page 5, line 6, wherein the quote in question reads "..."increase in intraocular fibrosis". Therefore Applicants' statement of factual inaccuracy is erroneous and Applicants' arguments regarding such statements are moot.

Claims 22, 23, 25 and 26 are rejected under 35 U.S.C. 103 as being unpatentable over Connor as applied to claims 21 and 24 above, and further in view of MacKay. Claims 21 and 24 were rejected for reasons as stated above. MacKay discloses the relationship between TGF-beta and the proliferation of glomerular cells and the accumulation of mesangial matrix in progressive glomerular nephritis. It would have been obvious to one of ordinary skill to substitute glomerular tissue for the ocular tissue of Connor in order to obtain a method of treating pathologies characterized by an accumulation of extracellular matrix once the ability of the antibody to block TGF-beta activity was successfully demonstrated. It would have been obvious to apply the concept to diseases characterized by excess TGF-beta production and having increased extracellular matrix production since the ability of the antibody to bind to TGF-beta is irrespective of tissue location or cell type, lacking evidence to the contrary.

Regarding claims 22 and 25, glomerular nephritis is a progressive disease of glomerular cells, which are a part of the kidney tissue.

Regarding claims 23 and 26, it would have been obvious to one of ordinary skill to apply the treatment of Connor to other diseases characterized by overproduction of extracellular matrix and have a

reasonable expectation of success once the basis of the diseases had been recognized as being TGF-beta induced, lacking evidence to the contrary.

McKay provides the motivation to combine the references on page 1160, Abstract, wherein it is stated "The presence of TGF-beta receptors on intact glomeruli and on each glomerular cell type and the demonstrated responsiveness of these cells to TGF-beta combine to suggest that potentially important interactions may occur between resident glomerular cells and TGF-beta in vivo". Thus, it would have been obvious to one of ordinary skill to use an antibody to TGF-beta in order to interfere with the interaction between TGF-beta and glomerular cells in an in vivo setting since antibodies are known to be able to localize to particular tissues in vivo.

Accordingly, the modification of the method of Connor by using the antibody to treat tissues suffering from glomerular nephritis as suggested by MacKay in order to obtain a method for treatment of pathologies characterized accumulation of extracellular matrix in a tissue was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 28 is rejected under 35 U.S.C. 103 as being unpatentable over Flanders as applied to claim 27 above, and further in view of McKay. Claim 27 was rejected under 35 U.S.C. 102(b) for reasons as stated above. MacKay discloses that mesangial cells possess TGF-beta receptors (Abstract) and further discloses that TGF-beta significantly increased the production of proteoglycans in mesangial cells.

It would have been obvious to one of ordinary skill to substitute the mesangial cells of MacKay for the NRK cells of Flanders in order to obtain a

method of decreasing the production of a TGF-beta induced proteoglycan in view of the teachings of Flanders that proteoglycan production was decreased and MacKay that mesangial cells had TGF-beta receptors. Note that both mesangial cells and NRK cells are kidney cells and therefore one of ordinary skill would have had a reasonable expectation of success in decreasing the production of a TGF-beta induced proteoglycan in mesangial cells as well once production was shown to be decreased in NRK cells, lacking evidence to the contrary. Flanders discloses antibodies to TGF-beta which block binding of TGF-beta to its receptors. It would have been obvious to one of ordinary skill to use antibodies in the method of Flanders to block the binding of TGF-beta to its cellular receptors in order to decrease production of a TGF-beta induced proteoglycan in a mesangial cell since MacKay clearly shows that TGF-beta is necessary for the production of the proteins.

Accordingly, the modification of the method of Flanders by substituting the mesangial cells as suggested by MacKay in order to obtain a method of decreasing the production of a TGF-beta induced proteoglycan by a cell was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 29 is rejected under 35 U.S.C. 103 as being unpatentable over Flanders as applied to claim 27 above, and further in view of Bassols. Claim 27 was rejected under 35 U.S.C. 102(b) for reasons as stated above. As previously stated, Flanders discloses use of the antibody to TGF-beta to block TGF-beta induced collagen production in NRK cells, collagen being another proteoglycan. Bassols discloses that NRK cells produce, in response to TGF-beta, large amounts of a proteoglycan PGI, identified in the specification (page 14) as also being known as biglycan, and a second proteoglycan PGII,

also known as decorin . Bassols therefore discloses that NRK cells produce biglycan and decorin in response to TGF-beta stimulation. It would have been obvious to one of ordinary skill in view of the teachings of Flanders that treatment of NRK cells with antibodies to TGF-beta would likewise inhibit the production of biglycan and decorin as was seen with collagen.

Accordingly, the modification of the method of Flanders by detecting decreases in the production of biglycan and decorin as suggested by Bassols in order to obtain a method of decreasing the production of a TGF-beta induced proteoglycan by a cell was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants have argued that MacKay fails to cure the deficiencies of Connor and that Applicants have explained the deficiencies of MacKay in their prior amendment and continue to stand by that position. However, the Examiner's previous remarks continue to be valid in rebuttal to Applicants' arguments.

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)308-4227.

An inquiry concerning this communication should be directed to Examiner Suzanne Ziska, Ph.D., at telephone number 703-308-1217.

SUZANNE E. ZISKA
PRIMARY EXAMINER
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6/1/94